Docket No.: 20022/42179
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Umberto Benatti et al.

Application No.: 10/584,874 | Confirmation No.: 7927

Filed: June 7, 2007 | Art Unit: 1654

For: Glutathione Derivatives and Their Uses for the Treatment of Viral Diseases | Examiner: R. T. Niebauer

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

This Appeal Brief is submitted in accordance with 37 C.F.R. § 41.37(a) and MPEP §1205.02 to support the Notice of Appeal filed in this application on December 28, 2009. This Appeal Brief is accompanied by the fee for filing an Appeal Brief under 37 C.F.R. §1.17(b) and a one-month extension of time under 37 C.F.R. §1.136(a). Accordingly, this Appeal Brief is timely filed and no further fees are believed due.

Any additional required fee may be charged, or any overpayment credited, to Deposit Account No. 13-2855.

II. TABLE OF CONTENTS

III. REAL PARTY IN INTEREST

The real party in interest in this appeal is FIRST S.r.l. (First), Rome, Italy, the assignee of the entire right, title, and interest to the above-identified patent application. The assignment was recorded in the United States Patent and Trademark Office ("USPTO") at Reel 23209, Frame 0400, on September 8, 2009, which constitutes the entire chain of title from the inventors to First.

IV. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellants, appellants' legal representative, or the assignee which will directly affect or be directly affected by, or have a bearing on, the Board's decision in the pending appeal.

V. STATUS OF CLAIMS

A. HISTORY

This application was originally filed with claims 1-14. Claims 15-28 were added to the application in a preliminary amendment.

B. CURRENT STATUS OF CLAIMS

Claims canceled: 1-14 and 16.

Claims withdrawn from consideration but not canceled: 19-22 and 24-28.

Claims pending: 15 and 17-28.

Claims allowed: None.

Claims rejected: 15, 17, 18, and 23.

C. CLAIMS ON APPEAL

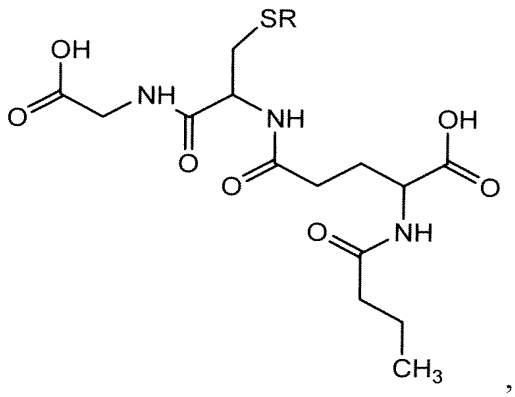
The claims on appeal are claims 15, 17, 18, and 23.

VI. STATUS OF AMENDMENTS

Appellants filed an after-final amendment and Request for Continued Examination on July 14, 2009. A final rejection then was issued on October 1, 2009, and a Notice of Appeal was filed on December 28, 2009. Accordingly, appellants understand that the current form of the claims are represented by the Amendment Accompanying Request for Continued Examination, filed July 14, 2009, and as reproduced in the Claims Appendix below.

VII. SUMMARY OF CLAIMED SUBJECT MATTER

The present invention is directed to a glutathione derivative having a formula:



,

wherein R is H or acetyl (independent claim 15).

The present invention also is directed to a medicament comprising a glutathione derivative of claim 15 (claim 17), wherein the medicament is an antiviral medicament (claim 18).

The present invention is further directed to a pharmaceutical composition comprising a glutathione derivative of claim 15, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, diluent, or mixture thereof (claim 23).

The claimed glutathione derivative of independent claim 15 is disclosed in the specification at page 1, lines 5-9 (as corrected in the amendment of October 9, 2008), page 4, lines 17-26, and in Fig. 1. The claimed glutathione derivatives contain a butanoyl-group ($-C(=O)CH_2CH_2CH_3$), and are referred to in the specification using the abbreviation GSH-C4 (specification, page 5, lines 14-16).

The claimed glutathione derivatives demonstrate antiviral activity, and hence are useful in medicaments and compositions.

VIII. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Whether claims 15, 17, 18, and 23 would have been obvious under 35 U.S.C. §103 over Anderson et al. U.S. Patent No. 5,464,825 ('825) in view of a McMurry publication (McMurry).

For purposes of the issues on appeal, claims 17, 18, and 23 are grouped and argued with claim 15.

IX. ARGUMENT

A. INTRODUCTION

Appellants submit that the rejection issued in the final Office Action is in error, and that the present application is in condition for allowance. Appellants respectfully request the Board to review and reverse the rejection issued in the final Office Action.

B. PROPER BASIS FOR A §103(a) OBVIOUSNESS REJECTION

A determination that a claimed invention would have been obvious under §103(a) is a legal conclusion involving four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations, if any, of non-obviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). Secondary considerations of non-obviousness include factors such as commercial success, long-felt but unresolved needs, the failure of others, and/or *unexpected results achieved by the claimed invention. Id.* Obviousness is determined from the vantage point of a hypothetical person having ordinary skill in the art which the claimed subject matter pertains, who is presumed to have all prior art references in the field of the invention available to him/her. In *re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998). Furthermore, obviousness must be determined as of the time the invention was made and in view of the state of the art that existed at that time. *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 837 F.2d 1044, 1050-51 (Fed. Cir. 1988).

The Patent Office must clearly articulate facts and reasons why the claimed invention "as a whole" would have been obvious to a hypothetical person having ordinary skill in the art at least as of the claimed invention's effective filing date. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007) (citing with approval In *re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) ("[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.")); see also MPEP §2143 ("The key to supporting any rejection under 35 U.S.C. §103 is the clear articulation of reason(s) why the claimed invention would have been obvious.").

To reach a proper determination under 35 U.S.C. §103(a), the examiner must step backward in time and into the shoes worm by the hypothetical "person of ordinary skill in the art" when the invention was unknown and just before it was made. In view of all factual information, the examiner then must make a determination whether the claimed invention "as a whole" would have been obvious at that time to that person. Knowledge of applicants' disclosure must be put aside in reaching this determination, yet kept in mind in order to determine the "differences," conduct the search, and evaluate the "subject matter as a whole" of the invention. The tendency to resort to "hindsight" based upon applicants' disclosure is often difficult to avoid due to the very nature of the examination process. However, impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the *facts* gleaned from the prior art. MPEP §2142.

As articulated by the Court of Appeals for the Federal Circuit in *Ortho-McNeil Pharmaceutical Inc. v. Mylan Laboratories Inc.,* 86 USPQ 2d, 1196, 1201-2 (Fed. Cir. 2008):

> "As this court has explained, however, a flexible TSM test remains the primary guarantee against a non-statutory hindsight analysis such as occurred in this case. *In re Translogic Tech., Inc.* 504 F.3d 1249, 1257 [84 USPQ 2d 1929] (Fed. Cir. 2007) ("[A]s the Supreme Court suggests, a flexible approach to the TSM test prevents hindsight and focuses on evidence before the time of invention.)."

Furthermore, to establish a prima facie case of obviousness, the examiner must satisfy three requirements. First, the prior art references must teach or suggest all the limitations of the claims. In *re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970). Second, as the U.S. Supreme Court held in *KSR International Co. v. Teleflex Inc. et al.*, 127 S.Ct. 1727 (2007), "a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. ...it [may] be necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was *an apparent reason* to combine the known elements in the fashion claimed by the patent at issue. ...it can be important to *identify* a *reason that would have prompted a person of ordinary skill in the relevant field to combine the elements* in the way the claimed new invention does...

because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." (emphasis added, *KSR*, *supra*). Third, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. *Amgen Inc. v. Chugai Pharm. Co.*, 18 USPQ2d 1016, 1023 (Fed. Cir. 1991).

Once the Patent Office properly sets forth a prima facie case of obviousness, the burden shifts to the applicants to come forward with evidence and/or argument supporting patentability. *See In re Glaug*, 283 F.3d 1335, 1338 (Fed. Cir. 2002). Rebuttal evidence is merely a showing of facts supporting the opposite conclusion." *In re Piasecki*, 745 F.2d 1468,1472 (Fed. Cir. 1984). Evidence rebutting a prima facie case of obviousness can include: (a) "evidence of unexpected results," *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 1369 (Fed. Cir. 2007); or (b) "evidence that the prior art teaches away from the claimed invention in any material respect," *In re Peterson*, 315 F.3d 1325, 1331 (Fed. Cir. 2003). The Patent Office must always consider such evidence supporting patentability. *See, e.g., In re Sullivan*, 498 F.3d 1345, 1352-53 (Fed. Cir. 2007).

To support an obviousness rejection, an examiner can rely upon an "obvious to try" rationale. To reject a claim based upon this rationale, the following must be articulated:

> "(1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;
>
> (2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;
>
> (3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and
>
> (4) whatever additional findings based on the G*raham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness."

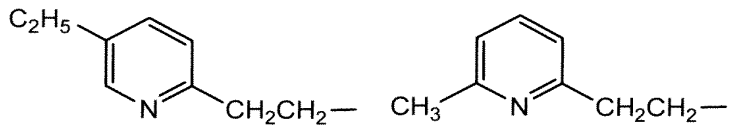
If any of these findings cannot be made, then the "obvious to try" rationale cannot be used.

As stated in *Takeda Chemical Industries v. Alphapharm Pty. Ltd.*, 492 F3d. 1350, 1356-7 (2007):

> "That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*. While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S.Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id. Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.*" (emphasis added)

The court then held that modifications to a prior art compound, including steps of homologation or ring-walking, *did not* render the specific new compounds obvious because nothing in the prior art provided a reasonable expectation that the modifications would be beneficial. Accordingly, even though the number of modifications were finite, the prior art failed to provide a reasonable expectation of success.

In *Takeda*, the claimed compound (A) was found non-obvious over a prior art compound (B), even though (A) and (B) have a similar structure and each has anti-diabetic activity. The court held that there was no reasonable expectation that the modification would reduce toxicity (492 F.3d at 1361-1362). In addition, a showing that the prior art would have suggested making the specific molecular modification necessary to achieve the claimed invention also is required (492 F.3d at 1356). For new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish *prima facie* obviousness of the new claimed compound (492 F.3d at 1357).



A B

Also, see *Sanofi-Synthelabo v. Apotex, Inc.* 470 F.3d 1368, wherein a specific salt form of a specific enantiomer of a compound was found non-obvious.

The Board also is directed to *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories, Inc.* 86 USPQ2d 1196 (Fed. Cir. 2008), for a discussion of the obvious-to-try rationale and avoiding hindsight analysis in deciding that a claimed compound would not have been obvious. Also, see *Eisai Co. Ltd. v. Dr. Reddy's Laboratories, Ltd.*, 87 USPQ2d 1452 (Fed. Cir. 2008), wherein a compound having ring substituent $-OCH_2CH_2CH_2OCH_3$ was found to be nonobvious over an identical prior art compound except for having a ring substituent of $-OCH_2CF_3$. As the court stated in *Eisai*, "[T]o the extent an art is unpredictable, as the chemical arts are, *KSR*'s focus on the 'identical, predictable solutions' may present a difficult handle because potential solutions are less likely to be genuinely predictable."

In addition, a contention of *prima facie* obviousness can be rebutted by evidence of advantageous properties unexpected from the prior art (*In re Merck*, 800 F.2d 1091, 1098 (Fed. Cir. 1986). The rebuttal evidence can be in the patent specification (*Knoll Pharmaceutical v. Teva*, 367 F.3d 1381, 1385 (Fed. Cir. 2004)), and the comparisons must be with the closest prior art (*In re Baxter Travenol Labs*, 952 F.2d 388, 392 (Fed. Cir. 1991)).

Finally, in the very recently decided case of *In re Chapman* (CAFC 2009-1270, Feb. 2010), the court noted errors made by the USPTO in interpreting a reference, and stated the following:

> "The government argues that these errors are harmless, but we conclude that these errors are harmful because they increase the likelihood that Chapman was erroneously denied a patent on grounds of obviousness. If the Board based its decision on a misunderstanding of Gonzalez, its conclusions regarding obviousness are called into question. With respect to

the second error, the Board was mistaken as to whether Gonzalez teaches the use of a polymer to link the light and heavy chains in a $F(ab')_2$ fragment in the cited embodiment. Therefore, Chapman's use of a polymer to link together two F(ab') fragments may be less likely to be obvious. Further, as to the third error, if the Board did not appreciate the full scope of antibody fragments disclosed in Gonzalez, we cannot be confident about its ultimate conclusion that the selection of one of them to form Chapman's molecule is obvious, as it appears that there are more possibilities from which to choose. Because we cannot say with confidence that the Board would have reached the same conclusion in the absence of these errors, we are persuaded they are indeed harmful. *See Kotteakos v. United States*, 328 U.S. 750, 765 (1946)."

C. REJECTION OF CLAIMS 15, 17, 18, AND 23 UNDER 35 U.S.C. §103 AS BEING OBVIOUS OVER ANDERSON ET AL. U.S. PATENT NO. 5,464,825 ('825) IN VIEW OF A MCMURRY PUBLICATION (MCMURRY)

Claims 15, 17, 18, and 23 stand rejected under 35 U.S.C. §103 as being obvious over Anderson et al. U.S. Patent No. 5,464,825 ('825) in view of a McMurry publication (McMurry). The rejection is based on this combination of references because the '825 patent teaches alkyl mono-esters of N-acyl glutathione that increase intracellular GSH levels and McMurry teaches ester hydrolysis. The examiner relies upon an "obvious to try" rationale to support the rejection, and concedes that neither reference expressly teaches the compound of the claimed invention (Office Action of October 1, 2009, page 4).

As stated in the Office Action of October 1, 2009at pages 5 and 6:

"In the instant case, the claims would have been obvious because 'a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product nor [sic] of innovation but of ordinary skill and common sense'. In particular, Anderson teach a finite number of compounds to be used (column 4 line 10-30). Further, Anderson specifically teach R1 values and teach that the R1 is hydrocarbon with preferably 1 to 3 carbons and can be propyl (column 4 line 44-48). One would recognize that the compound with R1 being hydrocarbon with preferably 1 to 3 carbons represents a finite number of possible compounds. Further, such compounds are described as being de-esterified and hydrolyzed. From the teachings of the references, it is apparent that one of ordinary

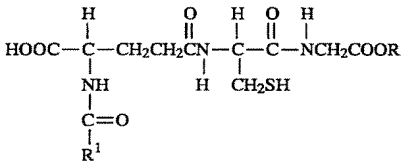
skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references."

Appellants traverse this rejection.

1. Disclosure of the '825 Patent and McMurry

The '825 patent discloses N-acyl glutathione monoalkyl esters as depicted at column 4, lines 9-18. As stated in the '825 patent at column 4, lines 3-32, in part:

"GSH has one amino group. GSH has two carboxyl groups, one on the glutamic acid residue and one on the glycine residue. The compounds used in the present method are alkyl esters of N-acetyl GSH in which only the glycine carboxyl group is esterified. Thus, the compounds used in the present invention have the structure:



N-acetyl GSH monoester

...

wherein R is an alkyl group containing 1 to 10 carbon atoms, and R^1 is hydrogen or an alkyl group containing 1 to 9 carbon atoms."

The '825 patent discloses increasing intracellular levels of GSH (glutathione) and GSH equivalents. However, this is accomplished *in vivo*, i.e., inside cells, by "administering *an alkyl mono-ester* of N-acyl glutathione, with the esterification occurring at the glycine carboxylic group" ('825 patent, column 3, lines 21-27)[1] by degrading the compounds by de-esterfication and deacylation to provide free GSH.

[1] The present claims do not recite an ester group on the glycine residue, but require a carboxyl group.

The '825 patent also discloses that the alkyl R group of the glycine ester can contain 1 to 10 carbon atoms, preferably 1 to 4 carbon atoms, with no apparent change in "GSH level elevating activity." In addition, the '825 patent discloses that the hydrocarbon portion of the acyl group, i.e., R^1, can contain 1-9 carbon atoms, and preferably 1-3 carbon atoms, also with no disclosed difference in GSH level elevating activity ('825 patent, column 4, lines 33-43).

The '825 patent describes the disclosed invention at column 3, lines 22-30 stating:

> "This invention relates to a method for increasing intracellular GSH levels or intracellular levels of glutathione equivalents i.e. N-acyl glutathiones or glutathione monoalkyl esters by *administering an alkyl monoester of N-acyl glutathione, with the esterification occurring at the glycine carboxylic acid group*. Such acylated esters are transported into cells, for example, liver and kidney cells and are de-esterified and de-acetylated within the cells, leading to increased cellular levels of GSH." (emphasis added).

The '825 patent fails to teach or suggest using a glutathione derivative having two carboxyl groups and the butanoyl group of the present claims. The sole example of the '825 patent is N-acetyl glutathione monoethyl ester. In fact, the '825 patent teaches that the *mono-ester* form is *necessary* to transport the molecule into the cells, i.e., '825 patent, column 7, line 56 through column 8, line 16 stating:

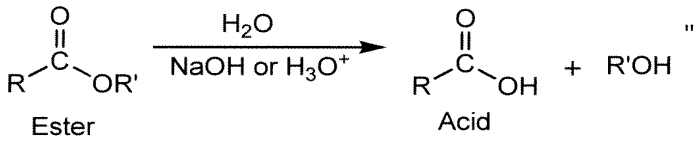
> "The findings disclosed herein indicate that *the administered N-acetyl GSH monoester is transported into* the cells of the liver and kidney where it is hydrolyzed to GSH; N-acetyl GSH and GSH monoester are also formed. The studies in which mice were pretreated with L-buthionine-SR-sulfoximine provide strong evidence for the transport of N-acetyl GSH monoesters; under these conditions, the synthesis of GSH from its constituent amino acids is markedly inhibited. Also the finding of N-acetyl GSH and GSH monoester in tissues *is strong evidence that N-acetyl GSH monoester is transported into cells and hydrolyzed*. It is *also seen that intact GSH is not delivered into the cell*, since GSH synthesis is markedly inhibited by L-buthionine-SR-sulfoximine. Thus, the present method permits increasing the intracellular GSH level in instances where a deficiency of the necessary synthetase for

GSH exists, or where a higher level of GSH or N-acetyl GSH is beneficial." (emphasis added)

The McMurry publication is simply a page from an elementary organic chemistry textbook showing a hydrolysis reaction providing a carboxylic acid from a corresponding ester. The totality of the teachings in the McMurry reference relied upon by the examiner is as follows:

"Hydrolysis: Conversion of Esters into Carboxylic Acids

Esters are hydrolyzed, either by aqueous base or by aqueous acid, to yield carboxylic acids plus alcohols:



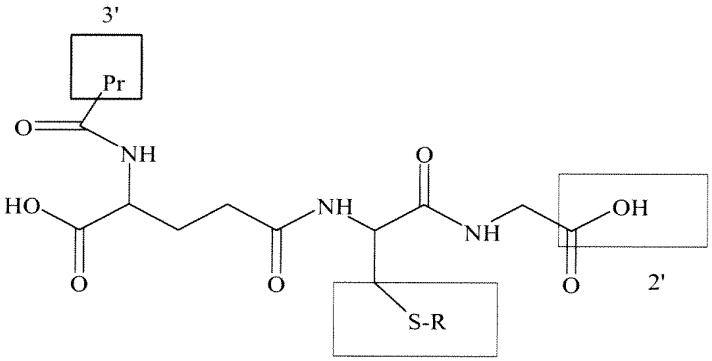
"

2. Non-obviousness of Claims 15, 17, 18, and 23

The '825 patent fails to render claims 15, 17, 18, and 23 obvious under 35 U.S.C. §103. In particular, the '825 patent fails to suggest the desirability of the modification leading to presently claimed invention with any reasonable expectation of providing a useful glutathione derivative. In addition, the presently claimed glutathione derivatives exhibit unexpected benefits that could not have been predicted from the modifications to the '825 patent proposed by the examiner.

The obviousness rejection of claims 15, 17, 18, and 23 is based on a combination of references wherein the '825 patent teaches alkyl mono-esters of N-acyl glutathione increase intracellular GSH levels and McMurry teaches ester hydrolysis. The examiner further relies upon an "obvious to try" rationale to support the rejection.

The present invention is directed to glutathione derivatives having the closely tailored structure of Compound B:

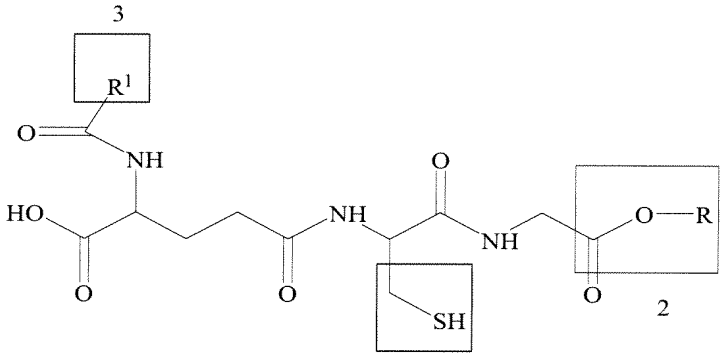


1' , (B)

wherein R can be H or acetyl.

Importantly, the claimed compounds *require* the carboxyl group of box 2' *and* the butanoyl group (C(=O)Pr) of box 3'. A claimed compound B also contains a second carboxyl group, and *lacks* an ester group.

The '825 patent discloses the following compound A:



1 (A)

wherein R can be C_1-C_{10} alkyl, preferably C_1-C_4 alkyl, and R^1 can be C_1-C_9 alkyl, preferably C_1-C_3 alkyl. The '825 patent discloses, for example, methyl, ethyl, propyl, butyl, pentyl, and hexyl as R^1 groups. The '825 patent fails to disclose that the R group of box 2 can be H, as presently claimed.

The examiner relies upon McMurry for teaching a simple desterification reaction that would lead to the carboxyl group at position 2' of compound B, thereby

rendering the present claims obvious. The examiner, however, is completely disregarding an important, and *essential*, feature of the '825 patent, *and* the unexpected benefits provided by the claimed compounds.

Compounds A and B each are N-acyl derivatives of glutathione (GSH), but compounds A and B have differences in structure with respect to the moieties in the highlighted boxes, i.e.,

(a) differences between boxes 2 and 2': present compound B has a carboxylic residue whereas '825 patent compound A has an ester residue;

(b) differences between boxes 3 and 3': present compound B is limited to a propyl group which is a selection among all the possible residues of the '825 patent compound A; and

(c) differences between box 1 and 1': '825 patent compound A has an hydrogen residue whereas present compound B can have a hydrogen or acetyl group.

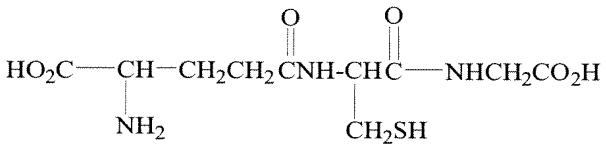
Focusing on the moieties in boxes 2 and 2', compound A of the '825 patent is an esterified derivative of claimed compound B, and a de-esterification reaction as disclosed in the McMurry publication could lead to claimed compound B. However, the cited '825 patent explicitly *discourages* such a de-esterification reaction to provide a compound B.

The '825 patent, at column 4, lines 17-27, provides a scheme illustrating the *in vivo*, i.e., *inside* cells (see '825 patent, column 3, lines 65-67), degradation of a compound A by de-esterification and deacylation, to provide free GSH. The '825 patent is directed to increasing intracellular levels of GSH and GSH equivalents, this is accomplished by "administering *an alkyl mono-ester* of N-acyl glutathione, with the esterification occurring at the glycine carboxylic group" ('825 patent, column 3, lines 21-27 *in vivo*). Increased intracellular levels of GSH is *not* accomplished by administration of a compound having *two* carboxyl groups, as claimed and as demonstrated below.

In fact, the '825 patent teaches that the N-acetyl GSH *mono-ester* form is *necessary* to transport the compound into the cells, i.e., '825 patent, column 7, line 56 through column 8, line 16 stating:

> "The findings disclosed herein indicate that *the administered N-acetyl GSH monoester is transported into* the cells of the liver and kidney where it is hydrolyzed to GSH; N-acetyl GSH and GSH monoester are also formed. The studies in which mice were pretreated with L-buthionine-SR-sulfoximine provide strong evidence for the transport of N-acetyl GSH monoesters; under these conditions, the synthesis of GSH from its constituent amino acids is markedly inhibited. Also the finding of N-acetyl GSH and GSH monoester in tissues is *strong evidence that N-acetyl GSH monoester is transported into cells and hydrolyzed.* It is *also seen that intact GSH is not delivered into the cell*, since GSH synthesis is markedly inhibited by L-buthionine-SR-sulfoximine. Thus, the present method permits increasing the intracellular GSH level in instances where a deficiency of the necessary synthetase for GSH exists, or where a higher level of GSH or N-acetyl GSH is beneficial." (emphasis added)

It is important to note that "intact GSH is not delivered into the cell" ('825 patent, column 8, lines 9-12), and that GSH has the structure



which includes *two* carboxyl groups.

The present claims do not recite an ester group on the glycine residue, but *require* a carboxyl group. In addition, as shown above, the '825 patent discourages, and leads a person skilled in the art away from, providing a presently claimed compound having two carboxyl groups and no ester group.

It also is well known to persons skilled in the art that even a slight modification in the structure of a compound can completely change the pharmacokinetics and bioavailability of the compound. The '825 patent teaches that it is *essential* to provide the

mono-ester compound A to effectively increase intracellular GSH levels. It cannot be predicted *a priori* that changing the ester moiety of the '825 patent to a carboxylic acid would provide a useful drug, especially in view of the teachings of the '825 patent which stresses the necessity of the mono-ester form of the compound. The '825 patent provides *no* suggestion to deviate from the mono-ester structure, and suggests that a modification of the ester group to a carboxylic acid group would lead to a compound that does not increase GSH levels in the cell, e.g., GSH.

In fact, the '825 patent demonstrates how a minor change in structure can have drastic effects on compound efficacy. The sole example of the '825 patent, i.e., N-acetyl GSH monoethyl ester, was compared to GSH for effects on glutathione levels in the liver and kidney (Example 1 and Comparative Example 1 of the '825 patent). Intracellular GSH levels in the liver were *not* effected by GSH (which contains two carboxylic acid groups like a claimed compound B), and only a slight effect was noted in the kidneys. From the structure above, GSH contains *two* carboxylic acid groups as claimed, and a drastic difference results in intracellular GSH levels by administering GSH versus the N-acetyl GSH monoethyl ester of the '825 patent (i.e., one carboxylic acid group and one methyl ester group).

In addition to stressing the necessity of a mono-ester compound, the '825 patent shows that no to low efficacy can result from a minor change in structure, in particular by de-esterifying the monoalkyl ester moiety. The '825 patent therefore further discourages individuals from modifying the disclosed mono-ester compounds in a way to arrive the presently claimed compounds because there is no reasonable expectation of providing a compound that increases intracellular GSH levels.

It could not have been predicted that converting the ester moiety of a compound of the '825 patent to a carboxylic acid moiety would provide a compound that effectively reaches the cells where the biological action is needed. It is well known that prodrugs, like those of the '825 patent, often perform better than the corresponding drugs because they have an improved bioavailability and/or are better able to reach the intended target site.

In contrast to the teachings of the '825 patent, and unexpectedly and unpredictably, the glutathione derivatives of claim 15 do *not* require an esterified glycine residue, but perform effectively when a *second* carboxyl group is present on this residue. The glutathione derivative of claim 15 also *requires* the propyl group of box 3' to achieve the benefits of the present invention. The '825 patent provides no teaching or suggestion that a compound of the present invention having the features of boxes 1', 2', *and* 3' of compound B could enhance intracellular GSH levels, but rather shows that GSH containing two carboxyl groups did *not* increase intracellular GSH levels, as discussed above (i.e., "intact GSH is not delivered into the cell").

In addition, the presently claimed compounds also do not rely solely upon a second carboxyl group on the glycine residue for enhanced activity. The propyl group of box 3' is important and necessary to achieve the enhanced activity of the present compounds. In particular, appellants have shown that an acetyl group (2 carbons) is inactive and alkanoyl groups of other lengths are of low activity or are toxic (i.e., alkanoyl groups with eight and twelve carbons). See specification, page 6, lines 14-21 and page 11, line 22 through page 12, line 15. These results could not have been predicted. These results also are unexpected and in direct contrast to the teachings of the '825 patent, wherein the carbon length from the '825 patent disclosure of the hydrocarbon group R^1 *apparently does not effect compound activity*, and the sole example contains an acetyl group. In the '825 patent, an acetyl group at R^1 increases intracellular GSH levels. However, contrary to this teaching in the '825 patent, an acetyl group in place of a claimed butanoyl group *destroys* the activity of the present compounds. This result also could not have been predicted from the teachings of the '825 patent, as required to support an obviousness rejection based on an obvious to try rationale. This result could not have been predicted from the teachings of the '825 patent.

With respect to the McMurry publication, this reference is merely a general teaching that esters can be hydrolyzed to acids. However, the primary '825 patent provides no incentive for a person skilled in the art to perform such a hydrolysis with any reasonable expectation of providing a GSH compound that *can enter* a cell to increase intracellular GSH levels (i.e., a mono-ester is required and GSH did not increase intracellular GSH levels). The only hydrolysis performed in the '825 patent is *in vivo*, and the '825 patent discloses that de-esterification *prior* to administration provides a GSH compound that does *not* work. In

particular, the '825 patent specifically teaches that the *mono-ester* is required to achieved the benefits of the invention and that "intact GSH" (which contains two carboxyl groups) is not delivered into the cell ('825 patent, column 8, lines 9-12). This is further demonstrated in the examples of the '825 patent, wherein glutathione (GSH), having two carboxyl groups, "had only a slight effect" ('825 patent, column 7, lines 14-19).

In addition, appellants respectfully note that MPEP §§2142 and 2143 require that the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on appellants' disclosure. *In re Vaeck*, 947 F.2d 4899 (Fed. Cir. 1991). The mere fact that the prior art may be modified in the manner suggested by the examiner does *not* make the modification obvious unless the prior art suggests the desirability of the modification. *In re Gordan*, 733, F.2d at 902, 221 USPQ at 1127. *In re Fritch*, 23 USPQ 2nd 1780, 1783-1784 (Fed. Cir. 1992). It is impermissible to use the claimed invention as an instruction manual or "template" to piece together the teachings of the prior art so that the claimed invention is rendered obvious. *In re Gorman*, 933 Fed. 2nd 982, 987, 18 USPQ 2nd 1885, 1888 (Fed. Cir. 1991). *In re Fritch*, 23 USPQ 2nd 1780 at 1784 (Fed. Cir. 1992).

The four requirements to support an obviousness rejection based upon an "obvious to try" rationale is set forth above at page 11. If *any* of these findings cannot be made, then the "obvious to try" rationale cannot be used.

The case law related to an obvious to try rationale is discussed above at pages 12 and 13. The decided cases teach that a minor change in structure cannot support an "obvious-to-try" rationale when the prior art fails to provide a reasonable expectation of success. For the reasons stated above, the modification suggested by the examiner would not provide a reasonable expectation of increasing intracellular GSH levels.

To arrive at the present invention, a skilled artisan would have had to make modifications to the '825 patent compounds that are neither taught nor suggested by the '825 patent, but rather are *discouraged* by the '825 patent. In particular, the '825 patent specifically teaches the need for a mono-ester, or else intracellular GSH levels are not increased or achieved only a slight effect. Accordingly, the '825 patent provides no reason

for a person skilled in the art to modify a compound of the '825 patent in a way to arrive at the presently-claimed compounds which contain two carboxylic acid groups *with any* reasonable expectation of substantially successfully increasing intracellular GSH levels.

There can be no reasonable expectation of success when the primary reference specifically shows that a compound with two carboxylic acid groups does *not* work, or works only marginally, whereas a mono-ester of the compound does. The '825 patent teaches success using a mono-ester that is de-esterified *in vivo*. A person skilled in the art may consider using the acid form of GSH because that is the pharmaceutically-active form, but the '825 patent shows that the acid form does *not* work or performed only marginally. For that reason, the '825 patent is directed to the mono-ester form of GSH. So where is the reasonable expectation of success by going back to the acid form (which the '825 patent discloses and shows does not enter the cell)?

In addition, if it arguably is obvious-to-try the acid form of the compound disclosed in the '825 patent, appellants further show that the *propyl group* at box 3' is *necessary* and that other chain lengths do not work. Appellants found that the N-acetyl analog of the claimed compounds *did not* perform (whereas the N-acetyl form of the '825 patent mono-ester compound did perform). Only the presently claimed N-butanoyl compounds demonstrated efficacy. In contrast, the N-acetyl *mono-esters* of the '825 patent (see Example) apparently perform well. These results further show how apparently relatively minor structural changes to a compound substantially alters compound efficacy, and cannot lead to a prediction of efficacy.

These findings further demonstrate the unexpected results provided by the present invention, which could not have been predicted from the disclosure of the '825 patent. The skilled person would have had *no* reasonable expectation of success from the proposed modifications that result in the claimed compounds. It is the appellants who found that the specific propyl group (box 3'), in combination with two carboxyl groups (e.g., box 2'), are able to enter cells and provide efficacious results. Varying any of these moieties will reduce or destroy these efficacious results. In particular, chains shorter or longer than propyl have been shown to be either ineffective or toxic. This discovery is in direct contrast to the

'825 patent, which requires a mono-ester and suggests that all alkyl chain lengths are effective.

It further must be noted that comparing a presently claimed compound to a compound of the '825 patent would have little to no value. If one assumes that the mono-ester compound disclosed in the '825 patent is efficacious (as disclosed), this comparison would show very little. The claimed compounds also have shown to be efficacious, and are entirely different compounds. The present invention does not reside in providing compounds better than those in the '825 patent, but resides in *different* compounds that *also* increase intracellular GSH levels, *and* wherein the presently claimed compounds have a structure that is discouraged by the '825 patent.

The '825 patent *itself* shows that a GSH derivative with two carboxylic acid groups does not perform compared to the mono-ester. In view of the '825 patent, it is unexpected that the claimed compounds perform at all.

In addition, appellants have shown that only the claimed butanoyl compound is useful. This is shown in the specification which compares compounds of different carbon lengths at the 3' position *and* having two -CO_2H groups. Therefore, the inventors *already* compared the claimed compounds to compounds *even closer in structure* (i.e., two carboxy groups and N-acyl with a chain length different from propyl) to the claimed compounds than compounds disclosed in the '825 patent (i.e., carboxy group, ester group, and N-acyl). See MPEP § 716.01(a), stating that the examiner must consider comparative data in the specification in making a conclusion of obviousness, and *In re Soni*. 54 F3d 746 (1995), wherein the court stated "[C]onsistent with the rule that all evidence of nonobviousness must be considered when assessing patentability, the PTO must consider comparative data in the specification in determining whether the claimed invention provides unexpected results." The court made it clear that such "factual evidence" in the specification must be considered and is different from "mere argument or conclusory statement" in the specification. In the case at bar, appellants have provided factual evidence comparing the claimed compounds to compounds even closer in structure to the claimed compounds than the compounds disclosed in the' 825 patent.

In summary, for all the reasons set forth above, appellants submit that claims 15, 17, 18, and 23 would not have been obvious under 35 U.S.C. §103 over a combination of the '825 patent and the McMurry publication, and that the rejection should be withdrawn. With respect to the examiner's obvious to try rationale, he has not meet his burden with respect to a reasonable expectation of success as a result of the proposed structural modification.

3. Response to Examiner's Comments in the Office Action

In the Office Action of October 1, 2009, the examiner makes several statements in an attempt to support the rejection. Appellants now rebut these statements.

(1) At page 12 of the Office Action, the examiner states:

> "Although Applicants argue that the '825 patent teach the need for the monoester, it is unclear where such information is stated in '825. In column 4 line 21 Anderson teach N-acyl GSH and then goes on to state that pharmaceutically acceptable salts of the above compounds, which include N-acyl GSH, are within the scope of the present invention (column 4 lines 30-32)."

The '825 patent is replete with disclosure showing the necessity of the mono-ester form. First, any disclosure relating to a salt form of a compound of the '825 patent refers to the carboxylic acid group that *has not been esterified.* With respect to where information is stated in the '825 patent relating to the necessity of a mono-ester, the Board is directed to no farther than the abstract. The Board also is directed to the following portions of the '825 patent, some of which have been quoted above: column 3, lines 22-44; column 3, line 65 through column 4, line 2; column 4, lines 9-18 and 28-49; column 4, line 49 through column 5, line 14 (synthesis of the monoester); column 5, lines 23-47 (administration of the monoester); Examples at column 5, lines 61 through column 8, line 16; column 8, lines 17-26 (other uses of the monoester); and the '825 patent claims. It is clear that the entire '825 patent is directed to the mono-ester form of an N-acyl GSH.

In addition, numerous times in the Office Action, the examiner states that the pharmaceutical salts of the compounds of the '825 patent are disclosed. This does *not* mean

that the '825 patent fails to require the mono-ester form of the compounds. The mono-ester GSH derivatives still contain only one carboxylic acid group, and it is *this* carboxylic acid group that is converted into a salt, *not* the ester group.

This is the type of misinterpretation of a reference addressed by the CAFC in *In re Chapman*, discussed above at pages 13 and 14. The examiner's misinterpretations clearly are not harmless, and call the examiner's conclusion regarding obviousness into question.

(2) At page 8 of the Office Action, the examiner states:

> "Although applicants argue that the prior art lead away, Section 2123 II of the MPEP expressly states that alternative embodiments are prior art and state that a composition does not become patentable because it has been described as somewhat inferior."

The '825 patent explicitly shows that a compound with two carboxylic acid groups results in "no effect" on glutathione levels in the liver and "only a slight" effect in the kidney (see column 7, lines 15-19). Also, "intact GSH did not enter the cell" ('825 patent, column 8, lines 9-12). This is substantially different from "somewhat inferior," rather it is described as essentially ineffective. This readily discourages persons skilled in the art from considering a GSH derivative having two carboxylic acid groups.

Section 2123 I of the MPEP states that "[A] reference may be relied upon for all that it would have *reasonably* suggested to one having ordinary skill in the art." An explicit teaching that a GSH having two carboxylic acid has no or "only a slight effect" reasonably suggests to a person skilled in the art to *avoid* such a compound, and rather use a mono-ester derivative as disclosed in the '825 patent.

(3) At page 8 of the Office Action the examiner further states:

> "Although Applicants argue that the prior art is directed to increasing intracellular levels of GSH and GSH equivalents, it is noted that the instant claims are drawn to compounds. The claims do not recite any information with respect to increasing any levels of any component or any other intended use."

It is well settled that a species can be patentable over a previous disclosed genus, i.e., a selection patent. Patentability resides on unexpected results demonstrated by the species. Even if the '825 patent arguably encompasses the claimed compounds, the unexpected results demonstrated by the claimed compounds overcome any contention of obviousness. First, the '825 patent teaches that a compound having two carboxylic acid groups has little to no effect, and that the mono-ester form is needed for *in vivo* conversion to increase GSH levels. The '825 patent therefore clearly leads persons skilled in the art away from a GSH derivative having two carboxylic acid groups. Second, appellants have found that a butanoyl group is required, and that other chain lengths for the alkanoyl group do not work. These results are unexpected and could not have been predicted *a priori* after considering the '825 patent. As a compound claim, functional recitations are not necessary in the claim.

(4) At page 9 of the Office Action, the examiner cites Section 2144.09 of the MPEP. However, although the claimed compounds may be structurally similar to the compounds of the '825 patent, rather than being suggested by the '825 patent, they are *discouraged*. The difference in properties is great because the '825 patent teaches that a mono-ester GSH derivative is needed for transport into the cell for conversion to GSH, and that administering GSH (having two carboxylic acid groups) has little to no effect. The benefit of the prior art is using a mono-ester GSH derivative capable of transport into a cell. Appellants have found that a mono-ester GSH derivative is not needed.

(5) At page 11 of the Office Action the examiner states:

> "Importantly, it is noted that Anderson does not teach in the examples any specific results with respect to the N-acyl GSH (column 4 line 24). Thus, without specific data for the N-acyl GSH there is not a basis to say that the N-acyl GSH does not work. Further, a single test using a single assay (as used in Anderson example 1) would not necessarily lead one to say that a compound is not effective."

The '825 patent provides no specific results for an N-acyl GSH compound because the references never considered or addressed using an N-acyl GSH compound. The '825 patent is directed to overcoming problems associate with compounds like GSH having

two carboxylic acid groups by using the mono-ester form. It is appellants that found the N-butanoyl GSH derivative has efficacy, and has a structure discouraged by the '825 patent.

(6) At pages 11-12 of the Office Action, the examiner states:

> "Although Applicants state that the sole example in '825 is for an acetyl group and carbon length apparently does not effect compound activity, it is unclear how applicants assert that carbon length does not effect activity yet at the same time assert that minor changes in structure can result in changes."

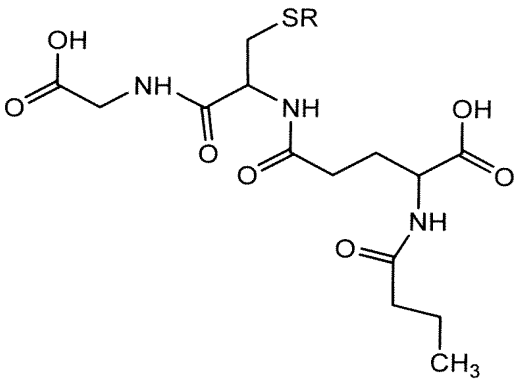
There is no inconsistency in appellants' argument. It cannot be denied that minor changes in structure can result in major pharmacological changes, e.g., thalidomide. If the examiner contends otherwise, such conjecture has not been supported. Further, appellants are giving the '825 patent the benefit of any doubt regarding efficacy of the disclosed compounds. The '825 patent discloses R groups containing up to 10 carbon atoms and provides an example that increases intracellular GSH levels. Accordingly, appellants can only assume that the compounds disclosed in the '825 patent are efficacious. The '825 patent has limited the scope of the compounds to those that presumptively are operative. Nevertheless, even if all compounds disclosed in the '825 patent are not operable, the present compounds *have a different structure*, and the '825 patent discourages persons skilled in the art from pursuing the presently claimed compounds.

(7) At page 12, the examiner states:

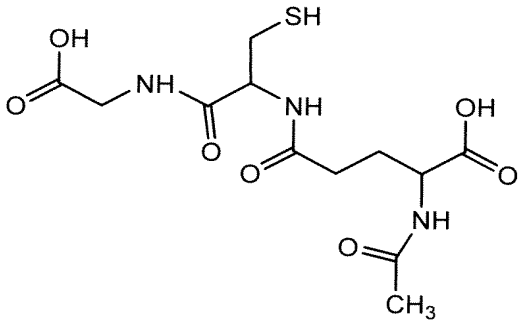
> "Importantly, it is noted that Anderson does not teach in the examples any specific results with respect to the N-acyl GSH (column 4 line 24). Thus, without specific data for the N-acyl GSH there is not a basis to say that the N-acyl GSH does not work. However, since N-acetyl monoethyl ester and even GSH alone cause at least slight effects, there is a reasonable basis that N-acyl GSH would cause effects."

The '825 patent has no results with respect to N-acyl GSH because, it is not addressed to an N-acyl GSH. The reference is addressed to mono-esters of N-acyl GSH that the particle *theorizes* hydrolyzes *in vivo* to N-acyl GSH. Appellants have not stated that an N-acyl GSH does not work, and cannot so state because the *claimed* compounds are N-

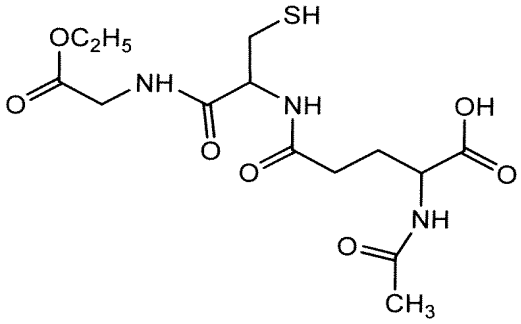
butanoyl GSH. Appellants do state and show in the specification that an N-acyl GSH different from N-butanoyl does not work (i.e., 2, 6, 8, and 12 carbon alkanoyl groups). Appellants also noted that the N-acetyl compound of the '825 patent increased GSH levels (see Example of the '825 patent), but that the very closely related N-acetyl compound of GSH (GSH-C2 of the present specification) did *not* work. This shows the unpredictability in the art *and* that a minor structural difference has major pharmacological impacts. The sole difference between GSH-C2 of the specification and Example 1 of the '825 patent is a $-CO_2H$ group vs. a $-CO_2C_2H_5$ group.



Claimed compound having efficacy (GSH-C4 in specification)



Compound in the specification lacking efficacy (GSH-C2 in specification)



Example 1 of '825 Patent that increase cellular GSH levels.

(8) At page 13 of the Office Action the examiner states:

"Although Applicants argue that the modification suggested by the examiner would not provide a reasonable expectation of increasing intracellular GSH levels, the schematic shown in column 4 of Anderson, expressly teach that

> N-acyl GSH is converted via deacylation to GSH. Thus N-acyl GSH is the immediate precursor to GSH. If the level of the immediate precursor (i.e. N-acyl GSH) is increased, there is a reasonable basis that GSH levels will increase."

The '825 patent clearly teaches that administration of GSH (containing two carboxylic acid groups) had "no effect" on liver GSH levels and "only a slight effect" on kidney GSH levels. Also, "intact GSH did not enter the cell. Accordingly, the '825 patentees discovered the mono-ester form that substantially increases GSH levels. " After reading the results of the '825 patent tests, where is the reasonable expectation of successfully increasing GSH levels by administration of a GSH derivative having two carboxylic acid groups. The examiner's conclusion that if the level of precursor N-acyl GSH is increased, then GSH levels will increase neglects to consider a very important fact. The GSH derivative must enter the cell. If it does not enter the cell, there is no conversion to GSH. If exogenous GSH entered cells effectively, there would be no need for *any* GSH derivatives.

(9) At page 15 the examiner states:

> " Although Applicants argue that the applicants have shown that an acetyl group is inactive and other lengths are of low activity or are toxic, it is noted that section 716.02(b) of the MPEP states that the burden is on the applicant to establish that results are unexpected and significant. In the instant case, Figures 1-3 appear to show results from a single compound which is depicted in figure 1 and called GSH-C4. Other compounds are discussed (i.e. GSH-C2, GSH-C6, GSHC8, GSH-C12) however the structures of such compounds are net set forth. In particular, page 7 lines 23-25 merely refers to these compounds as derivatives which were prepared with similar methods. Absent structural information on what was actually tested by applicants, it cannot be determined if the results are commensurate in scope with the claims (see MPEP section 716.02(b) III and 716.02(d))."

Appellants are claiming a compound designated GSH-C4 in the specification. The C4 stands for butanoyl (-C(=O)Pr) as the N-acyl substituent of GSH. The structure of the claimed compound is set forth above in paragraph (7) above at page 30. Appellants also synthesized the C2 (-C(=O)C_5H_{11}), C6 (C(=O)C_5H_{11}), C8 (-C(=O)C_8H_{17}) and

C12 (-C(=O)$C_{12}C_{25}$) N-acyl derivatives of GSH, i.e., GSH-C2, GSH-C6, GSH-C8, and GSH-C12, respectively.

GSH-C4 is identified at page 4, lines 17-20 of the specification. The examiner is directed to page 7, lines 23-28 of the specification that clearly identifies the C2, C6, C8, and C12 derivatives as ethanoyl, hexanoyl, octanoyl, and dodecanoyl. The structure of the derivatives are readily determined from the information in the specification contrary to the contention of the examiner, and it is clear which compounds were tested by appellants.

(10) At page 15 and 16 of the specification, the examiner questions the unexpectedness of the results in appellants' specification. The unexpected results and the unpredictability in the art has been fully addressed above. However, in short, because the *cited art* stresses the need for a mono-ester GSH derivative in order to increase intracellular GSH levels, it is unexpected that the N-acyl GSH derivatives as claimed (containing two carboxylic acid groups) should be so effective. Second, it is unexpected that only the C4 (butanoyl) compound provided efficacious results whereas shorter C2 (ethanoyl) and longer C6 (hexanoyl) acyl groups did not perform efficaciously or were toxic.

(11) At page 17 of the specification the examiner states:

> "It is noted that it appears that applicant may be attempting to show a criticality (compare MPEP 716.02(d) II) of the carbon chain length. However, Anderson expressly teach that the alkyl chain preferably contain 1 to 3 carbons (column 4 lines 44-47). Further, applicants specification state that GSH-C4 showed the best effects (page 12 lines 8-15). A showing of 'best effects' does not show that the range is 'critical'. In the instant case, when testing a group of compounds, one would expect that the compounds would not behave identically."

The specification at page 12, lines 8-15 states:

> "An inventive selection was then made between the various possible glutathione derivatives in order to find which ones could obtain the best effects as antiviral agents and it was surprisingly found that only with GSH-C4 derivatives according to formula I is it possible to obtain adequate antiviral efficacy and simultaneously solve the aforesaid problems correlated to the use of GSH."

The selection of the claimed GSH-C4 compounds was based on the tests and results set forth at pages 8-12 of the specification. All tested compounds except GSH-C4 were found unsuitable because of toxic effects and/or poor antiviral activity. Accordingly, appellants finely tuned the tested compounds to clearly and precisely claim the inventive compounds, while discarding very closely related compounds that lacked efficacy and/or were toxic.

X. CONCLUSION

In view of the foregoing remarks, appellants respectfully request that the Board reverse the final rejection of claims 15, 17, 18, and 23 and that all pending claims should be allowed.

Dated: March 25, 2010

Respectfully submitted,

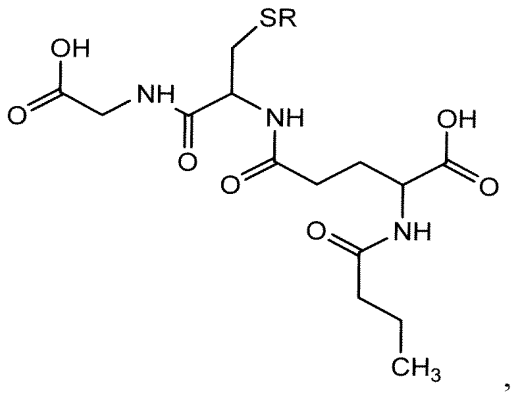
By _____
James J. Napoli
Registration No.: 32,361
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorney for Applicant

CLAIMS APPENDIX

Claims Involved in the Appeal of Application Serial No. 10/584,874

1.-14. (Cancelled)

15. (Previously presented) A glutathione derivative having a formula:



,

wherein R is H or acetyl.

16. (Cancelled)

17. (Previously presented) A medicament comprising a glutathione derivative of claim 15.

18. (Previously presented) The medicament of claim 17 wherein the medicament is an antiviral medicament.

19. (Withdrawn) A method of treating a disease caused by Paramyxoviruses comprising administration of an effective amount of a glutathione derivative of claim 15 to an individual in need thereof.

20. (Withdrawn) A method of treating a disease caused by Orthomyxoviruses comprising administration of an effective amount of a glutathione derivative of claim 15 to an individual in need thereof.

21. (Withdrawn) A method of treating a disease caused by Herpes Simplex-1 comprising administration of an effective amount of a glutathione derivative of claim 15 to an individual in need thereof.

22. (Withdrawn) A method of treating a disease caused by HIV comprising administration of a glutathione derivative of claim 15 to an individual in need thereof.

23. (Previously presented) A pharmaceutical composition comprising a glutathione derivative of claim 15, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient, diluent, or mixture thereof.

24. (Withdrawn) A method of treating a virus infection comprising administration of an effective amount of a glutathione derivative of claim 15 to an individual in need thereof.

25. (Withdrawn) The method of claim 24 wherein the virus infection is caused by Paramyxoviruses.

26. (Withdrawn) The method of claim 24 wherein the virus infection is caused by Orthomyxoviruses.

27. (Withdrawn) The method of claim 24 wherein the virus infection is caused by Herpes simplex-1.

28. (Withdrawn) The method of claim 24 wherein the virus infection is caused by HIV.

EVIDENCE APPENDIX

None.

RELATED PROCEEDINGS APPENDIX

There are no related proceedings.